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Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries

Michal Schwartz and Jonathan Kipnis

Neuronal degeneration after traumatic injury to the central nervous system (CNS) can be reduced by active immunization or passive transfer of T cells against CNS-associated myelin antigens. We propose that a protective autoimmunity is evoked by CNS insult when non-immunological local protective mechanisms cannot adequately buffer the injury-induced toxicity. The ability of a particular strain to develop a protective autoimmune response appears to be inversely related to its susceptibility to autoimmune disease. We also propose that vaccination with specific CNS-derived 'safe' (non-pathogenic) peptides after traumatic CNS insult, and possibly at any stage of chronic neurodegenerative disease, can be used to boost the protective autoimmunity and thereby to reduce further injury-induced damage. Such therapeutic vaccination ensures that the augmented beneficial autoimmunity will be free of accompanying disease.

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Traumatic injury to the central nervous system (CNS) inevitably results in a loss of neurons that is substantially greater than might be expected from the severity of the injury[1]. This is because the insult triggers a cascade of events, starting with degeneration of the directly affected neurons and the consequent creation of a toxic extracellular micro-environment around the damaged nerve, leading to the eventual (secondary) degeneration of neurons that escaped the initial injury[2–4]. This sequence of events can explain the progressive loss of neurons seen after CNS trauma, as well as in chronic degenerative diseases after the primary risk factors are removed (for example, after alleviation of high intra-ocular pressure in glaucoma)[5]. Recognition that secondary degeneration is a feature of both acute and chronic degenerative disorders has directed the focus of research in neurotrauma toward seeking ways to arrest the spread of damage, with the dual aim of preserving at least some function and promoting repair.

In the search for ways to stop the spread of damage, several approaches have been adopted. One common approach seeks to neutralize the mediators of toxicity or interfere with their action[6–8]. Another is based on attempts to increase the resistance of spared neurons to the toxicity of their environment[9,10]. Research from our laboratory has taken a different approach. We seek to identify physiological mechanisms of self repair and find ways to simulate or boost them[11]. Recently we discovered that compounds emerging from damaged nerves alert the adaptive immune system, evoking a protective autoimmune response. In our view, because this response to trauma is physiological in character, boosting it is likely to exploit the body's own mechanisms of healing, and thus provide the most natural, comprehensive, and effective form of protection.

Protective autoimmunity: a physiological response

It is generally accepted that in all systems of the body, invasion by pathogens triggers the protective and defensive functions of the immune system. The immune activity operates by creating memory T cells that might be cytotoxic to the pathogen or might activate effector cells (macrophages or B cells). In the CNS, however, because of its status as a site of 'immune privilege' (where immune activity is thought to be minimal)[12], invasion by pathogens occurs to a very limited extent, if at all. The

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traditional view, therefore, is that the CNS, having little or no need for an adaptive immune response against pathogens, is poorly equipped for it. Likewise, with regard to trauma in the CNS, or any CNS degenerative conditions not involving pathogens, the general belief was that there is no need for adaptive immune activity, and indeed that any immune activity is bad, rather than good, for the affected individual[13,14].

Our studies showed that systemic injection of T cells directed against CNS myelin-associated proteins such as myelin basic protein (MBP) resulted in an increase in the number of accumulating T cells, and – in apparent correlation – an improvement in the rate of neuronal survival after traumatic CNS injury. Interestingly, systemic injection of T cells directed against a non-self protein such as ovalbumin resulted in a similar increase in the number of accumulating T cells with no neuroprotective effect[15–17]. The observed ability of the autoimmune T cells to reduce the post-traumatic neuronal loss was confirmed both morphologically and functionally using two different models of axonal trauma in rodents – the optic nerve and the spinal cord[18–21]. A beneficial effect was also observed using T cells directed against a peptide that is derived from MBP, but is not pathogenic, or a synthetic polymer that cross-reacts with a self protein, suggesting that the neuroprotective autoimmune response does not have to be pathogenic to be effective[15,22].

Studies in our laboratory showed that protective autoimmunity is a physiological response to CNS injury, and that in rats or mice devoid of mature T cells (owing to either neonatal thymectomy or transgenic modification) the rate of neuronal survival after crush injury of the optic nerve is significantly lower than in normal animals[23]. Further studies showed that the survival rate of retinal ganglion cells (RGCs) after optic nerve trauma is increased in rats over expressing a T-cell receptor for MBP. These findings led to the suggestion that trauma in the CNS evokes a self-protective T-cell-mediated autoimmune response that is presumably designed to counteract the damage, and without which the loss is more severe[24]. This suggestion is in agreement with the recently reported finding that recovery of motor neurons after facial nerve injury is worse in mice devoid of functioning T and B cells[25,26].

The possible existence of a physiological beneficial autoimmunity evoked by a CNS insult raises more questions. Is this autoimmunity present in every individual and under all circumstances? If not, what controls it?

Inverse relationship between the ability to exhibit protective autoimmunity and the susceptibility to autoimmune disease development

We examined the recovery from optic nerve injury in several strains of rats and mice differing in their susceptibility to the development of experimental autoimmune encephalomyelitis (EAE)[27,28] – a CNS-associated autoimmune disease that resembles multiple sclerosis in humans. Animals susceptible to the development of EAE were found to have only a limited ability to manifest a spontaneous protective autoimmune response to CNS insult, and their rate of post-injury neuronal survival was therefore lower than in EAE resistant animals[23]. Animals of a particular strain are defined here as 'resistant' to autoimmune disease development if they do not develop a disease upon active immunization with any of the myelin-associated self-proteins, and 'susceptible' if they develop the disease upon experimental challenge with at least one such protein. Using rodents that had undergone thymectomy at birth and consequently were devoid of mature T cells, we showed that the recovery from optic nerve injury was not better in the EAE-resistant strains, suggesting that recovery is limited to their ability to sustain a beneficial T-cell-dependent autoimmune response. In EAE-susceptible rodents devoid of T cells, recovery after a CNS insult was not worse than in the susceptible normal animals. These findings suggest that all individuals are capable of experiencing an anti-self response to trauma, and that this response, when suitably controlled, is beneficial. Our subsequent studies suggest that protective autoimmunity requires the participation of both anti-MBP T cells and some regulatory T cells. The presence of the first without the second might lead to lack of protection and even to destruction. Thus, in adult Lewis rats that were subjected to thymectomy at birth (and are therefore devoid of endogenous T cells, in particular regulatory T cells[29–31]), passive transfer of anti-MBP T cells after optic nerve injury still leads to EAE development but – unlike in rats with a normal thymus – not to protection of the damaged optic nerve (Kipnis, J. et al., unpublished). The injected autoimmune CD^+ T cells can activate other effector cells such as other $CD4^+$, $CD8^+$, M and B cells (Fig. 1). It is unlikely that the injected T cells interact directly with the damaged tissue, as antigen recognition by these cells requires its presentation in the context of MHC class II. They might, however, activate other invading or locally activated immune cells, some of which might in turn interact directly with the damaged neurons and thus help determine their fate. The failure of MBP-reactive CD4 T cells to elicit a neuroprotective response to optic nerve injury when injected into thymectomized rats strongly supports the hypothesis that these autoimmune T cells, though essential for neuroprotection, are not sufficient, and that the presence of endogenous regulatory T cells is also required. This hypothesis might explain the observed correlation between beneficial autoimmunity and the lack of susceptibility to EAE, as it is likely that the better outcome of CNS injury and the prevention of disease development are governed by the same

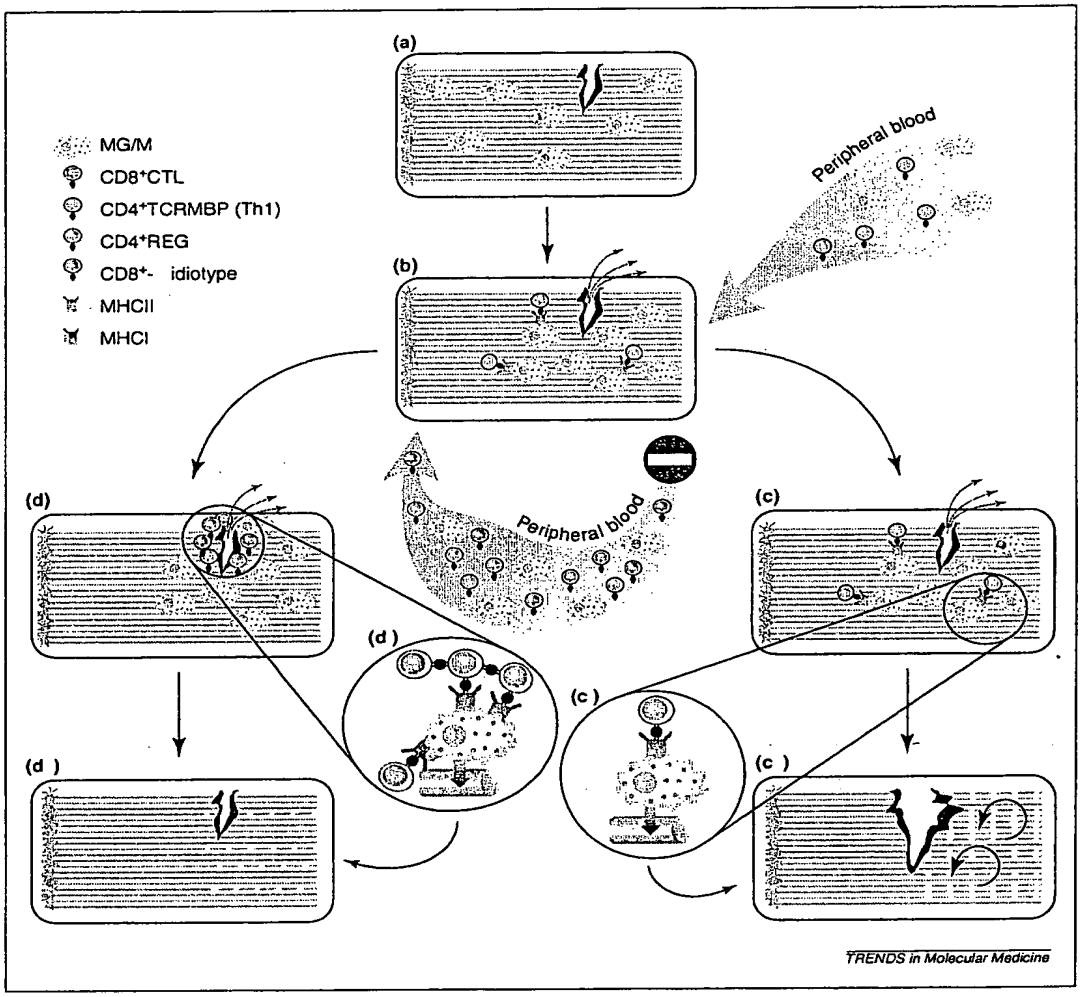

Fig. 1. Scheme depicting the events leading to protective autoimmunity. Protective autoimmunity is a multicellular and multifactorial process, involving recruitment of macrophages and activation of microglia, recruitment of T cells directed against myelin-associated proteins and peptides, and recruitment of CD4 and CD8 regulatory T cells. Malfunctioning of any step along this cascade leads to failure of protection and consequent progression of degeneration. (a) CNS axonal injury; (b) Stress signals from the damaged CNS tissue activate resident microglia, and recruit and activate blood derived macrophages as well as CD4 T cells directed against myelin proteins. A multi-cellular dialogue leads to neuroprotection; (c) In the absence of the regulatory response, self-destructive processes are not prevented and neurons continue to die as a consequence of secondary degeneration; (c) In the absence of additional T cells recruited from the periphery, there is no neuroprotection and the tissue degenerates; (c) The process of secondary degeneration progresses; (d) Interaction between CD4 T cells reactive to myelin proteins and the activated microglia/macrophages triggers further signals, resulting in recruitment of additional T cells (CD8 T cells specific to myelin proteins and CD4 –CD8 T cells with regulatory phenotypes) and macrophages to the protective network; (d) Microglia/macrophages via their dialogue with CD4 T cells, on one hand, and with regulatory CD4 T cells, on the other, are protective. The immune response is terminated by CD8 anti-idiotypic T cells; (d) The process of secondary degeneration is attenuated.

regulatory machinery. It is thus possible that in EAE-susceptible strains, unlike in resistant strains, the timing of onset of the anti-MBP T-cell response in relation to the activity of regulatory T cells does not correspond with the post-traumatic therapeutic window.

As discussed above, it is possible that the autoimmune response evoked by passive transfer or active immunization with myelin-associated antigens requires the participation of multiple cell types, including anti-MBP T cells and CD4 regulatory cells. It is also possible that the same T-cell population displays different activities depending on the tissue context, and that in the presence of damaged neuronal tissue (as in the case of the Lewis rats described above) such T cells might exert neuroprotection. This latter possibility obtains some support from the recent finding that neurons can derive benefit from protective substances originating in T cells, even if the T cells are encephalitogenic[32–34].

Table 1. Beneficial adaptive immune responses: when the response is beneficial, its absence is harmful

Stress signal	Normal response	Defective response
Infectious agent, infection	Protective immunity	Recurrence
Tumor	Tumor immunity	Cancer
Injurious conditions: trauma, degenerative disorders (oxidative stress, free radicals, increased excitatory amino acids, etc.)	Neuroprotective autoimmunity	Accelerated neuronal degeneration and predisposition to autoimmune disease

It should be noted that the same type of correlation between resistance to autoimmune disease and the ability to sustain a beneficial T-cell-dependent response to trauma was observed when the CNS insult was biochemical rather than mechanical. Thus, RGC survival in rats or mice after intravitreal injection of glutamate was correlated with susceptibility to autoimmune disease

Protective autoimmunity as a mechanism for homeostasis in the CNS

Taken together, our findings in connection with neuroprotective autoimmunity appear to ascribe a hitherto unrecognized function to the immune system. Up until now the adaptive immune response has been viewed as a defensive mechanism that evolved to provide a versatile backup when the innate immune response (involving macrophages) is unequal to the task. In this capacity, several activities have been attributed to it, and any malfunctioning of this adaptive response was assumed to be harmful for the individual[35]. Our studies provide evidence that stressful conditions, at least in the CNS, caused by a pathological increase in potentially toxic compounds (e.g. glutamate), might prove too overwhelming for the nervous system to cope, and thus alert the adaptive immune system (expressed here by the response to self-antigens) to provide neuroprotective immunity. In other words, autoimmune neuroprotection can be viewed as a mechanism for recruitment of a second line of protective activity when the local control mechanism is insufficient for the purpose. An inadequate autoimmune response will lead, on the one hand, to a lack of beneficial autoimmunity and hence accelerated degeneration, and on the other hand to destructive autoimmunity and hence a predisposition to autoimmune disease (Table 1). This pattern of immune inadequacy can be compared to the breakdown of the normal protective immune response in the face of an overwhelming infective process, resulting in recurrence of the infection. It can also be likened to a failure of the protective immune response against tumors, leading to cancer. Our finding of a physiological protective autoimmunity raises some fundamental questions in connection with the clonal deletion theory. Is beneficial autoimmunity a reflection of the positive selection of T cells to certain self proteins[36]? If so, autoimmune response would be expected to occur in all strains and individuals including those that are resistant to autoimmune diseases and not only in those that are susceptible. The main factor determining whether or not an individual will derive the benefit of protective autoimmunity without concomitant risk of autoimmune disease would then be the effectiveness of control by regulatory T cells.

Autoimmunity, traditionally always associated with autoimmune disease, has been attributed to auto-antigen-specific T cells that failed to undergo a process of negative selection. Studies in the 1990s reported intrathymic expression of several genes, including the gene encoding MBP, related to different organ-specific 'autoimmune diseases'[37,38]. These findings implied the existence of intrathymic mechanisms for clonal deletion of MBP-specific T cells, and autoimmune diseases were therefore assumed to result from an escape of autoreactive T cells from the process of negative selection. Subsequently, however, autoreactive T cells (in particular those directed against CNS antigens) were found in the blood of healthy individuals as well as of patients with multiple sclerosis, with no evidence to indicate that their numbers are higher in the latter[39,40]. The explanation offered was that these T cells are activated in some individuals (thus mediating the disease) but not in others.

We suggest that the presence, observed even in healthy individuals, of T cells directed against CNS myelin-associated proteins reflects not an escape of negative selection but rather a positive selection of T cells. A recently proposed additional function of the thymus is the peripheral regulation of autoimmune T cells[29,40]. Accordingly, we propose the following cascade of events: CNS trauma triggers an immune response in the form of T cells directed against myelin proteins. The autoimmune T cells are attracted to the site of injury, where they activate macrophages as a first step in a multi-step beneficial process. If the necessary regulatory machinery is operational, the process is completed and undamaged neurons survive. If, however, the regulatory mechanisms are malfunctioning, or the recruitment and activation of the various cells occur in a non-optimal time sequence, the process cannot proceed and neuronal degeneration continues (Fig. 1).

This proposed scenario raises questions about the etiology of autoimmune disease. Do autoimmune diseases, at least in the CNS, have a non-autoimmune etiology? If so, do they originate in local CNS damage of exogenous or endogenous origin, for which autoimmune assistance is recruited but is not effective in those individuals who do not possess all of the physiological machinery for autoimmune neuroprotection? If the latter suggestion is correct, it might be appropriate to view autoimmune diseases as the result of malfunctioning autoimmunity. This view would appear to be in

agreement with the finding that in a model of multiple sclerosis mediated by Theiler's murine encephalomyelitis virus (TMEV), accumulation of T cells in plaques protects neurons from demyelination. Depletion of these T cell subsets in resistant mice results in induction of demyelination and persistence of the virus[42,43].

This proposed explanation raises a new question. Do these findings run counter to darwinian evolution? According to that theory, a destructive feature, even if it has a beneficial side effect, would not be preserved, but would be transformed through natural selection into a beneficial feature and the destructive component would disappear; alternatively, the feature would disappear altogether. We suggest, however, that destructive autoimmunity can be accommodated by evolutionary dogma mutated 'beneficial autoimmunity'.

T-cell-based therapeutic vaccination

The above observations led to further questions. Might vaccination after CNS injury be a way to protect individuals from the devastating effects of secondary degeneration? If so, would vaccination be beneficial for all individuals, including those who enjoy endogenous beneficial autoimmunity (manifested, for example, by resistance to autoimmune disease)? In our early studies of the role of autoimmune T cells in recovery after CNS trauma, T cells directed against MBP were passively transferred into Lewis rats – strain susceptible to EAE. As mentioned above, neuroprotection was demonstrated in these rats after optic nerve crush or spinal cord contusion, despite the development of transient EAE (Refs 17,19). It should be noted that (1) no recovery was obtained when spinally contused rats were systemically injected with anti-MBP antibodies rather than with anti-MBP T cells, or (2) when anti-MBP T cells were transferred to rats with completely transected rather than partially injured spinal cords[19]. These findings indicate (1) that protective autoimmunity is derived from T cells, not from antibodies, and (2) that it is not an effective means of promoting regenerative growth (though we cannot rule out the possibility that recovery as a result of such protection includes some sprouting from the rescued tissue).

It is well-accepted that preventive vaccination places the immune system on call for action, thus shortening the lag period between invasion of a particular microorganism and recruitment of the specific immune cells needed to fight it. Vaccination is not a preventive measure, in the sense that it does not stop the microorganism from invading, but it endows the individual with protection by making it possible for the immune system to cope with the consequences of the invasion promptly and appropriately.

An analogous situation arises when the insult is caused by non-invaders. Just as conventional preventive vaccinations cannot repel microorganisms or alter the environment which they inhabit, there is no vaccination that will prevent a motor accident or a head trauma – yet here too, therapeutic vaccination might ensure speedy recruitment of the immune system by preparing it to protect the individual from the pathological consequences of the trauma. Both types of vaccination are based on eliciting a response by the immune system to the offending stimulus or antigen. When the vaccination is designed to protect the body from invaders, the antigen targeted by the immune response is the invading microorganism itself. When the vaccination is designed to protect the individual from insult-induced endogenous toxicity, the antigen is a self protein and the reaction elicited is therefore an autoimmune response. We can therefore view the immune system in general as the body's collective mechanism of defense against foreign antigens, and autoimmunity as the body's defense mechanism against specific self antigens. The question is: how can an autoimmune response be boosted safely? Is there a way to immunize with self antigens without the risk of introducing an autoimmune disease?

Vaccination with 'safe' antigens

Non-encephalitogenic antigens

In view of the versatility of human major histocompatibility complex (MHC), is it possible to select a 'safe' (non-pathogenic) antigen for therapeutic neuroprotection in human patients? One approach is to use a non-encephalitogenic epitope. Such epitopes exist in any self-antigen. However, because the encephalitogenic property is a function of the specific presentation of the epitope by the antigen-presenting cells, which is genetically determined by the individual's MHC, an epitope that is cryptic in one individual will not necessarily be cryptic in another. An alternative approach, analogous to conventional vaccination using attenuated microorganisms, is to modify the pathogenic self peptide in a way that renders it non-pathogenic. Another option is to select an antigen that can cross-react with a relevant self antigen but is known to be completely safe. In screening CNS injury-associated proteins for a safe antigen to boost the endogenous response to spinal cord injury, we also examined the post-traumatic effect of peptides that, though originally encephalitogenic, were modified by the replacement of a single amino acid in their T-cell receptor-binding site, a manipulation that attenuated the pathogenic effect[44–47]. A single vaccination with these peptides, immediately after spinal cord contusion in rats, exerted a neuroprotective effect, manifested by reduction of the injury-induced paralysis with no signs of autoimmune disease (Hauber, E. et al., unpublished). In patients with multiple sclerosis, however, the use of such peptides at high dosages might aggravate the disease[45,46].

Non-self polymers

Another way to vaccinate safely is to use synthetic compounds that are non-pathogenic and cross-react with myelin-associated self-antigens such as MBP. One such compound is the synthetic copolymer-1 (Cop-1) – an FDA-approved drug used as an immunosuppressant in multiple sclerosis. The suppression of EAE and MS by Cop-1 is thought to be the result of Cop-1-mediated suppression of pathogenic T cells (immune suppression)[48,49]. However, recent studies have suggested that the Cop-1 effect might be caused by immune modulation (by bystander suppression) rather than immune suppression[48]. Passive or active immunization with Cop-1 was shown in our laboratory to lead to significant protection of the visual system from mechanical insults and from glutamate toxicity[22,50]. We suggest that T cells that are reactive to Cop-1 might be activated by cross-recognition with myelin proteins at the site of the injury and consequently act like T cells that are reactive to myelin proteins. Alternatively, it is possible that the observed survival of neurons results from Cop-1-mediated modulation of the endogenous immune response. It should be noted that immune neuroprotection with Cop-1 was achieved in both EAE-resistant and EAE-susceptible strains of mice and rats, suggesting that Cop-1 might both boost the beneficial endogenous neuroprotective response that exists in resistant strains and stimulate this response in susceptible strains[22,50]. Studies in our laboratory have shown that immune neuroprotection from glutamate insults can be achieved by stimulating or boosting an endogenous beneficial autoimmune response[22,50]. Because active or passive immunization with Cop-1 provided efficient neuroprotection in animal models of mechanical or biochemical insults, it might be possible to overcome the antigen specificity barrier (resulting from factors yet to be determined) by using Cop-1. Because immunization with Cop-1 is protective against glutamate toxicity, a common mediator of toxicity in neurodegenerative disorders, it is potentially a powerful vaccination against degeneration induced by a wide range of insults in which the injury-induced toxicity is mediated by glutamate.

Conclusions

Our studies suggest that CNS insult evokes a protective autoimmunity, which enables the body to cope with the potential toxicity of self-compounds that are common to most CNS disorders and might cause cell death when their physiological levels rise. However, the ability to evoke a protective autoimmunity is genetically controlled and is inversely related to susceptibility to autoimmune disease development. Protective autoimmunity, the body's own response to a CNS insult, requires the integrated operation of various immune cells. This protective mechanism is analogous to the protective immunity that develops in response to stress of non-self origin. In principle, boosting of the protective autoimmunity by therapeutic vaccines is needed in order to slow down or stop the progressive degeneration seen in neurodegenerative diseases. It also implies that if a neurodegenerative disorder were diagnosed as an autoimmune disease, this would mean a priori that the affected individual has little or no ability to produce a beneficial autoimmune response.

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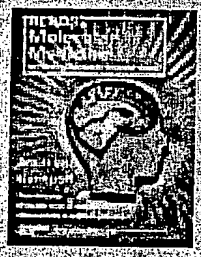

Welcome on board!

We welcome George C. Tsokos on the editorial board of *TMM*.

George Tsokos has a longstanding interest in the molecular understanding of systemic lupus erythematosus, rheumatoid arthritis and other autoimmune disorders, and in developing possible treatment strategies based on this understanding. His current appointments include Director of the Division of Immunology and Rheumatology, Dept of Medicine, Uniformed Services University of the Health Services, Bethesda, and Chief of the Dept of Cellular Injury, Walter Reed Army Institute of Research, Bethesda. He also carries out various editorial roles on the *Journal of Investigative Medicine*, *Clinical Immunology*, *Clinical and Diagnostic Laboratory Immunology* and *The Journal of Immunology*.